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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/881,535	06/14/2001	Vasulinga T. Ravikumar	ISIS-4785	8150

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EXAMINER	
EPPS, JANET L	

ART UNIT	PAPER NUMBER
1635	11

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/881,535	Applicant(s) RAVIKUMAR, VASULINGA T.	
	Examiner Janet L Epps-Ford, Ph.D.	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *17-32 and 37-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 33-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-16 and 33-36 in Paper No. 10 is acknowledged. The traversal is on the ground(s) that searching all the claims combined would not impose a serious burden on the examiner since Groups I and II are drawn to related subject matter and are classified as being in the same class and subclass. This is not found persuasive because the inventions of groups I and II are drawn to patentably distinct methods for preparing chemically different oligonucleotides, comprising different method steps and utilizing distinct reagents.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-16 and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook et al. (US Patent 6,440,943) in view of Barany et al. (US 5,852,168) and Eleuteri et al. (US Patent. 6335439).

The instant claims recite a method for preparing an internucleotide phosphorothioate linkage enriched in the Sp enantiomer between a synthon having a hydroxyl moiety at the 5'-position and a 2'-substituted nucleoside having an activated phosphate moiety at the 3'-position comprising selecting a coupling reagent having a pKa ranging from about 3.3 to about 4.5 and

coupling said synthon to said 2'-substituted nucleoside in the presence of said coupling reagent; wherein said coupling reagent is 5-(ethylthio)-1H-tetrazole; wherein said 2'-substituent is O-alkyl; and further wherein said activated phosphate moiety comprises a beta-cyanoethyl or an acetoxy phenoxy ethyl group.

Cook et al. teach the synthesis of Sp chirally pure phosphorothioate oligonucleotides comprising reacting an activated nucleoside synthon with the 5'-OH group of a nucleoside attached to a solid support (see for example, Example 21). Although, Example 21 utilizes 2'-deoxynucleoside (see compound 18), the invention of Cook et al. also comprises the use of 2'-O-protected nucleosides in the method for synthesizing chirally pure oligonucleotides. See for example, col. 8 (lines 25-42), wherein the 2' position of the nucleoside synthon (denoted as R1) comprises an H, hydroxyl, a protected hydroxyl, a 2'-substituent group, or a protected 2'-substituent group. In preferred embodiments, each R1 is a C1 –C10 O-alkyl or C1 -C10 substituted O-alkyl, with 2'-O-methoxyethyl or 2'-O-methyl being more preferred.

However, the method of Cook et al. does not comprise wherein the coupling agent has a pKa ranging from about 3.3 to about 4.5, wherein said coupling agent is 5-(ethylthio)-1H-tetrazole, or wherein the activated phosphate moiety comprises an acetoxy phenoxy or beta-cyanoethyl phosphate protecting group.

Barany et al. teach the synthesis of phosphorothioates comprising the use of 5-ethylthio-1H-tetrazole as the activator for the coupling of beta-cyanoethyl-ribonucleoside phosphoramidites to a controlled pore glass solid support loaded with the 3'-end of a ribonucleoside residue (the attachment of the 3'-end is indicative that the coupling reaction occurred with the 5' end of the attached ribonucleoside). Barany et al. teach that 5-ethylthio-1H-

tetrazole was used since it has greater acidity and solubility in acetonitrile than tetrazole. (see col 18, lines 5-35).

Eleuteri et al. teach the use of acetoxy phenoxy ethyl and beta-cyanoethyl as phosphorus protecting groups useful for protecting phosphorus containing internucleoside linkages during solid state oligonucleotide synthetic regimes (col. 5, lines 48-51).

It would have been obvious for one of ordinary skill in the art to modify the teachings of Cook et al. with the teachings of Barany et al. to devise a method for synthesizing a phosphorothioate oligonucleotide enriched with the Sp enantiomer comprising the use of 5-ethylthio-1H-tetrazole as the activator for coupling of nucleoside residues in phosphorothioate oligonucleotide synthesis. One of ordinary skill in the art would have been motivated to make this modification because Barany et al. teach that 5-ethylthio-1H-tetrazole is a suitable activator for phosphorothioate synthesis, and it performs the same function as the DBU activator used in the method of Cook et al. It is prima facie obvious for ordinary skilled artisan to substitute one functionally equivalent activator for another in the synthesis of the same class of molecules, in particular phosphorothioate oligonucleotides. Moreover, although Barany makes no mention of the pKa of 5-ethylthio-1H-tetrazole, absent evidence to the contrary, 5-ethylthio-1H-tetrazole inherently possesses a pKa of between 3.3 and 4.5.

Additionally, it would have been obvious for one of ordinary skill in the art at the time of filing to modify the teachings of Cook et al. with the teachings of Eleuteri et al. to produce a method for synthesizing phosphorothioates comprising the use of activated monomers comprising a phosphate moiety that is activated with an acetoxyphenoxy ethyl or beta-cyanoethyl protecting group. One of ordinary skill in the art would have been motivated to make

this modification in order to prevent unwanted side reactions with the substituents of the phosphate moieties of the individual monomers during the successive coupling reactions, additionally, Eleuteri et al. teach that these protecting groups aare well suited for protecting phosphorus containing internucleoside linkages during solid state oligonucleotide synthetic regimes.

Therefore the invention as a whole is *prima facie* obvious over Cook et al. in view of Barany et al. and Eleuteri et al.

Information Disclosure Statement

4. Applicant's Information Disclosure Statement submitted 7-24-01 was separated from the application file jacket, it is requested that Applicants provide a second copy so that the cited references can be properly considered by the examiner.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
December 30, 2002

SEAN McGARRY
PRIMARY EXAMINER